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Patty Wilson  
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: LeCluyse, Edward L., et al.

Group Art Unit: 1651

Serial No.: 09/527,352

Examiner: Afremova, V.

Filed: March 17, 2000

Docket No.: 421/17/2

For: METHOD OF SCREENING CANDIDATE COMPOUNDS FOR  
SUSCEPTIBILITY TO BILIARY EXCRETION

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SUPPLEMENTAL FILING

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

This is a supplemental filing for the subject U.S. patent application. Favorable reconsideration and allowance are respectfully requested in view of the following Remarks.

REMARKS

Status Summary

Claims 67-200 are now pending in the subject U.S. Continued Prosecution Application (CPA). Claims 67-200 as filed the instant CPA were subjected to a Restriction/Election Requirement. In a Response filed by facsimile on May 27, 2003, applicants elected the claims of Group III, claims 105-118, for prosecution at this time. Reconsideration of the present CPA based on the Declaration enclosed herewith and the arguments set forth below is respectfully requested.



Discussion of the Previously Cited Liu et al.[CC] Reference

Enclosed please find a Declaration of Dr. Kim L.R. Brouwer Pursuant to 37 C.F.R. Sections 1.131 and 1.132. This Declaration is believed to establish that the intended subject matter of claims 105-118 was invented prior to the publication date of a previously cited abstract: Liu et al. (1998) Pharm. Sci. 1:S-119 (referred to hereinafter as Liu et al. [CC]). The enclosed Declaration includes an exhibit, **Exhibit B**, that predates the Liu et al. [CC] abstract and that describes determination of a biliary clearance value for a xenobiotic compound in a hepatocyte culture as recited in claims 105-118.

Allowance of claims 105-118 over the Liu et al. [CC] abstract is therefore respectfully requested.

Discussion of the Previously Cited Combination of

LeCluyse et al.[U] and/or Liu et al.[EE]

in view of Liu et al.[EE], Poole et al.[V], and Dunn et al. [A]

The following combination was previously cited under 35 U.S.C. Section 103 in the prosecution of present U.S. CPA: LeCluyse et al. (1994) Am. J. Physiol. 266:C1764-C1774; Liu et al. (1997) Pharm. Res. 24:S-459; U.S. Patent No. 5,602,026 to Dunn et al.; Liu et al. (1996) Pharm. Res. Init. 13:S-393 (8003); and Poole et al. (1990) Archives of Toxicology 64:474-481 (hereinafter referred to respectively as: LeCluyse et al. [U]; Liu et al. [EE]; Liu et al. [DD]; Poole et al. [V]; and Dunn et al. [A]). Applicants respectfully submit that elected claims 105-118

are patentably distinguished over this combination based on the following arguments.

Independent claim 105 of elected claims 105-118 recites a method for screening a xenobiotic compound *in vitro* for susceptibility to biliary excretion *in vivo* by calculating a biliary clearance value for the xenobiotic compound. In particular, step (e) of claim 105 recites calculating a biliary clearance value.

LeCluyse et al. [U], Liu et al. [EE], Liu et al. [DD], Poole et al. [V], and/or Dunn et al. [A], when taken individually or in any combination thereof, do not teach, suggest, or motivate a method for determining susceptibility of a xenobiotic compound to biliary excretion *in vivo* using a biliary clearance value.

LeCluyse et al. [U] describes only detection of the presence or absence of a compound in a biliary canaliculus, but does not teach any quantitative determination of such detection. LeCluyse et al. [U] discloses only the use of fluorescein as a vital stain to demonstrate that the canaliculi are sealed. Thus, LeCluyse et al. [U] is merely concerned with showing a method of culturing hepatocytes to form canalicular networks so as to attempt to provide a representative model to study hepatic morphology and physiology.

Dunn et al. [A] does not teach any evaluation of biliary excretion. Liu et al. [EE], Poole et al. [V], and Liu et al. [DD] measure biliary excretion in terms of a biliary excretion index, a percentage of radiolabeled hormone accumulation, and  $K_m$  and  $V_{max}$ , respectively. However, in contrast to the methods of the present invention, Liu et al. [EE], Poole et al. [V], and Liu et al. [DD] did not determine a biliary clearance value. Thus, the biliary clearance value recited in claim 105 is

clearly distinct from each of the indicators of biliary excretion described by Liu et al. [EE], Poole et al. [V], and Liu et al. [DD].

Applicants respectfully direct the Patent Office's attention to Figure 6B of the subject U.S. patent application as filed. In Figure 6B, a linear correlation of *in vitro* biliary clearance to *in vivo* biliary clearance is established. See also page 38, lines 6 through 8, which further describe the correlation between *in vivo* intrinsic biliary clearance and *in vitro* biliary clearance.

Additionally, aspects of biliary clearance are discussed at page 20, lines 1 through 9 of the subject U.S. patent application as filed. Applicants therefore respectfully submit that this evidence clearly demonstrates the distinguishing features of the biliary clearance value over the approaches employed in the art of record.

Based on the foregoing arguments, claim 105 is believed to be patentably distinguished over the art of record in that LeCluyse et al. [U], Liu et al. [EE], Liu et al. [DD], Poole et al. [V], and Dunn et al. [A] fail to teach the above-discussed elements of the present invention. Claims 106-118 are dependent upon claim 105. Therefore, applicants respectfully submit that dependant claims 106-118 are likewise patentably distinguished over the proposed combination of LeCluyse et al. [U] and/or Liu et al. [EE] in view of Liu et al. [DD], Poole et al. [V], and Dunn et al. [A]. Allowance of claims 105-118 is also respectfully requested.

### CONCLUSION

In light of the above Remarks, it is respectfully submitted that the present application is now in a proper condition for allowance and such action is earnestly solicited. If any minor issues should remain outstanding after the Patent Examiner has had an opportunity to study the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney so that all such matters may be resolved and the application be placed in a condition for allowance without the necessity for issuance of another Official Action.

### Deposit Account

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS & WILSON, P.A.

Date: May 28, 2003

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Enclosures: Brouwer Declaration with Exhibits A-C  
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